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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/701,265	11/04/2003	Brenda F. Baker	ISIS-5300	7033
32650 7590 07/14/2010 WOODCOCK WASHBURN LLP CIRA CENTRE, 12TH FLOOR 2929 ARCH STREET PHILADELPHIA, PA 19104-2891				
EXAMINER				
PTTRAK, JENNIFER S				
ART UNIT		PAPER NUMBER		
1635				
MAIL DATE		DELIVERY MODE		
07/14/2010		PAPER		

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/701,265

**Applicant(s)**

BAKER ET AL.

**Examiner**

JENNIFER PITRAK

**Art Unit**

1635

**Period for Reply** -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 07 April 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 120, 121, 124, 127 and 136-138 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 120, 121, 124, 127, and 136-138 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Remarks***

Applicant's Pre-Appeal Brief Request for Review filed on 04/07/2010 resulted in the reopening of prosecution in this case as indicated in the Notice of Panel Decision from Pre-Appeal Brief Review mailed 04/30/2010. Any rejections of record that are not presented herein are withdrawn.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 120, 121, 124, 127, and 136-138 are pending and are under examination.

### ***Inventorship***

In view of the papers filed 08/18/2009, the inventorship in this nonprovisional application has been changed by the deletion of Brenda F. Baker, Anne B. Eldrup, Muthiah Monoharan, Balkrishen Bhat, Richard H. Griffey, and Eric E. Swayze.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

***Summary of the claims***

The claims are directed to a duplex of first and second chemically synthesized 17-25-nucleotide long oligonucleotides wherein the first oligonucleotide is 100% complementary to the second oligonucleotide and to a target mRNA, the two oligonucleotides are not covalently linked to each other, and the first oligonucleotide is a gapmer having at least 4 ribonucleosides (2'-hydroxy-pentofuranosyl sugar moiety) in the gap and having each wing comprising a 2'-sugar modification (claim 120). Claim 124 limits claim 120 to wherein at least one of the wings of the gapmer comprises a 2' sugar modification selected from fluoro, alkoxy, amino-alkoxy, allyloxy, imidazoylalkoxy, and methoxyethoxy. Claim 127 limits claim 120 to wherein each nucleoside of the 3' wing of the gapmer comprises a 2'-OCH<sub>3</sub>. Claims 136 and 137 limits claim 120 to the duplex wherein at least one or each of the oligonucleotides comprises at least one phosphorothioate linkage, respectively. Claim 121 limits claim 120 to wherein the second oligonucleotide is also a gapmer having at least 4 ribonucleosides and 2'-modified wings. The first support for the instant claims is provided in parent document US Application 08/870,608, now US Patent 6,107,094, at Example 27a (columns 50-51 of the patent), where such duplexes were disclosed as useful for studying double-stranded ribonuclease enzymes.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 120, 121, 124, 127, and 136-138 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wyatt et al. (Nucleic Acids Research 1989, vol. 17, pages 7833-7842), Manche et al. (Molecular and Cellular Biology 1992), Monia, et al. (1993, J. Bio. Chem., v.268:14514-22), and Shibahara, et al. (European Patent Application 0339842, published on 11/02/1989).

At the time the invention was made, those in the art routinely synthesized short duplexes containing ribonucleotide residues for the purpose of studying the activity and structural requirements of enzymes that bind or cleave nucleic acids. This is demonstrated by the teachings of Wyatt, et al., Manche, et al., and Monia, et al.

Wyatt et al. teach that sensitivity of DNA and RNA to nucleases depends upon both chemical and conformational differences. For example, the 2'-OH makes ribonucleotides susceptible to alkaline hydrolysis and cleavage by ribonucleases, a mechanism not available for cleavage of deoxynucleotides. Wyatt et al. further teach that RNase VI is a widely used probe for double-stranded RNA that does not have a specific requirement for 2'-OH and is thus postulated to be like RNase H, which cleaves RNA-DNA duplexes. To probe the structural requirements of RNase VI and RNase H, Wyatt et al. synthesized a series of 14-nucleotide duplexes wherein 2'-deoxyribonucleotides were site-specifically incorporated to allow study of duplexes containing covalently linked deoxy and ribo-nucleotides. These duplexes contain a sequence complementary to the ADCK2 gene (pages 7837-9).

Manche et al. teach that the protein kinase DAI, the double-stranded RNA- activated inhibitor of translation, is a pivotal cellular regulatory enzyme that is an important element in the

host antiviral response. Despite its importance as a regulatory enzyme, the interactions between DAI and its RNA effectors were complicated and incompletely understood. To better understand these interactions Manche et al. analyzed interaction of the enzyme with RNA duplex molecules of specified sizes ranging from 15-104 nt (see figure 1 ) to study binding and protection of dsRNA as well as activation and inhibition of the kinase.

Monia, et al. used a duplex to study the ability of a first oligonucleotide to direct RNase H cleavage *in vitro* and for antisense activity against Ha-ras (p.14516, 4<sup>th</sup> paragraph; Figure 1; p.14518, Figure 4; p.14520, Figure 6). The duplex comprises first and second chemically synthesized 17-25-nucleotide long oligonucleotides wherein the first oligonucleotide is 100% complementary to the second oligonucleotide and to a target mRNA and the two oligonucleotides are not covalently linked to each other (page 14516, 4<sup>th</sup> and 5<sup>th</sup> paragraphs and Figure 1). The first oligonucleotide is a 17-mer gapmer having phosphorothioate linkages, at least 4 deoxyribonucleosides (DNA) in the gap, and each wing comprising 2'-OMe-modified nucleotides. The second oligonucleotide is a 25-mer synthetic oligoribonucleotide (RNA) that is a portion of Ha-ras mRNA. The first oligonucleotide has 100% complementarity to Ha-ras and to the second oligonucleotide.

While Wyatt, et al., Manche, et al., and Monia, et al. demonstrate that production of short RNA-containing duplexes was routine in the art for the purpose of studying enzymes that bind or cleave nucleic acids, these references do not explicitly teach duplexes wherein a first oligonucleotide is an RNA gapmer and the references do not explicitly teach duplexes wherein both strands of the duplex are RNA gapmers.

Shibahara, et al. teach antisense oligoribonucleotides (RNA) for target mRNA (HIV) inhibition wherein the oligoribonucleotides comprise 2'-OMe-modified nucleotides (claim 1; pages 13-14). At page 4, Shibahara, et al. teach antisense oligonucleotides comprising phosphorothioate linkages and both ribonucleotides (RNA) and 2'-OMe-modified nucleotides, wherein the positions of RNA and the 2'-OMe-modified nucleotides are not specified and can be at any position within the oligonucleotide (see page 4, General Formula 1 and the definitions of X, X<sub>1</sub>, Y<sub>1</sub>, Q, and Q<sub>1</sub>). At page 13, Shibahara, et al. indicate that the invention is an improvement over DNA antisense oligonucleotides in that 2'-O-methylribooligonucleotides are resistant to various nucleases, including RNase H and DNases, and they form duplexes with complementary RNAs that are more stable than DNA-RNA duplexes (last paragraph on page 13 to top of page 14). Shibahara, et al. also indicate that 2'-O-methylribooligonucleotides are less expensive to prepare than are deoxyoligonucleotides (end of the paragraph spanning pages 13 and 14). Shibahara, et al. indicate that while the compounds of their invention show potent anti-AIDS activity, the mechanism of the activity has not been experimentally proven (page 15, lines 15 and 16).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make synthetic ribonuclease substrates wherein the substrate is an artificial duplex of a target RNA and a 2'-OMe-nucleotide-containing oligonucleotide because it was well known by those of skill in the art to study enzymes with such artificial substrates. It would have been obvious to use an artificial duplex of a target RNA and a 2'-OMe-nucleotide/RNA gapmer because Shibahara, et al. teach that 2'-OMe-nucleotide/RNA oligonucleotides are an improvement over DNA antisense oligonucleotides and because Monia, et al. teach antisense

oligonucleotides having 2'-OMe-nucleotide/DNA oligonucleotides. One of skill could substitute RNA for DNA in the gapmer of Monia, et al. and would be motivated to do so to study the mechanism of action of the 2'-OMe-nucleotide/RNA antisense oligonucleotide of Shibahara, et al., such as by testing the duplexes as substrates for various dsRNases, while protecting the oligonucleotide from exonucleases. One of skill in the art would further be motivated to modify the target RNA strand of the duplex with 2'-OMe-modified nucleotides to prevent unintended nuclease degradation of the target strand during such studies. One of skill would be motivated specifically to modify the ends of the target and antisense oligonucleotides, such as in a gapmer pattern with two 2'-OMe-modified nucleotides at the 3'- and 5'-ends, so as to increase the stability of the oligonucleotides by protecting the oligonucleotides from exonucleases. One of skill would also recognize that maintaining an unmodified RNA gap in the target strand would best simulate the *in vivo* condition of the target. Therefore, the claims would have been *prima facie* obvious to one of skill in the art at the time the instant invention was made.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 120, 121, 124, 127, and 136-138 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 130-156 of copending Application No. **10/859825** in view of Wyatt et al. (Nucleic Acids Research 1989, vol. 17, pages 7833-7842), Manche et al. (Molecular and Cellular Biology 1992), Monia, et al. (1993, J. Bio. Chem., v.268:14514-22), and Shibahara, et al. (European Patent Application 0339842, published on 11/02/1989). This is a provisional obviousness-type double patenting rejection.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the 10/859825 application are generic to the instant claims, which are rendered obvious by the teachings of the prior art as indicated in the rejection under 35 USC § 103(a).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 120, 121, 124, 127, and 136-138 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 86-123 of copending Application No. **10/701264** in view of Wyatt et al. (Nucleic Acids Research 1989, vol. 17, pages 7833-7842), Manche et al. (Molecular and Cellular Biology 1992), Monia, et al.

(1993, J. Bio. Chem., v.268:14514-22), and Shibahara, et al. (European Patent Application 0339842, published on 11/02/1989). This is a provisional obviousness-type double patenting rejection.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the 10/701264 application are generic to the instant claims or overlap in scope with the instant claims, which are rendered obvious by the teachings of the prior art as indicated in the rejection under 35 USC § 103(a).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER PITRAK whose telephone number is (571)270-3061. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Pitrak  
Examiner  
Art Unit 1635

/Richard Schnizer/  
Primary Examiner, Art Unit 1635